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Review Article

The pathogenesis of traumatic coagulopathy

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Summary

Over the last 10 years, the management of major haemorrhage in trauma patients has changed radically. This is mainly due to the recognition that many patients who are bleeding when they come in to the emergency department have an established coagulopathy before the haemodilution effects of fluid resuscitation. This has led to the use of new terminology: acute traumatic coagulopathy, acute coagulopathy of trauma shock or trauma-induced coagulopathy. The recognition of acute traumatic coagulopathy is important, because we now understand that its presence is a prognostic indicator, as it is associated with poor clinical outcome. This has driven a change in clinical management, so that the previous approach of maintaining an adequate circulating volume and oxygen carrying capacity before, as a secondary event, dealing with coagulopathy, has changed to haemostatic resuscitation as early as possible. While there is as yet no universally accepted assay or definition, many experts use prolongation of the prothrombin time to indicate that there is, indeed, a coagulopathy. Hypoxia, acidosis and hypothermia and hormonal, immunological and cytokine production, alongside consumption and blood loss, and the dilutional effects of resuscitation may occur to varying extents depending on the type of tissue damaged, the type and extent of injury, predisposing to, or amplifying, activation of coagulation, platelets, fibrinolysis. These are discussed in detail within the article.

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Introduction

Trauma remains a major cause of global morbidity and mortality, accounting for over 10% of deaths, with the majority due directly or indirectly to bleeding [1, 2]. Over the last 10 years, the management of major haemorrhage in trauma patients has changed radically. This is mainly due to the recognition that many patients who are bleeding when they come to the emergency department have an established coagulopathy before the dilutional effects of fluid resuscitation. Traumatic coagulopathy has been demonstrated in patients who received little or no intravenous fluid therapy, negating the long-held belief that iatrogenic haemodilution is the main causative factor in traumatic coagulopathy [3–6]. This has led to the use of new terminology: acute traumatic coagulopathy (ATC); acute coagulopathy of trauma shock or trauma-induced coagulopathy. In this review, we will use the term ATC. The recognition of ATC is very important because we now understand that its presence is a prognostic indicator, as it is associated with poor clinical outcome [7]. This has driven change in clinical management, so that the previous approach of maintaining an adequate circulating volume and oxygen carrying capacity before, as a secondary event, dealing with coagulopathy, has changed to haemostatic resuscitation as early as possible. However, the type of haemostatic resuscitation varies, with the USA giving

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fresh frozen plasma, while there is a different approach in Europe, led by Austria, where fibrinogen concentrates are used and supported by other factor products. The divergence in clinical practice reflects our limited understanding of ATC and comparisons between approaches need to be addressed in clinical trials.

The range of bleeding injuries is wide, and one has to question whether injuries from civilian, compared with military, trauma result in similar haemostatic changes. Military casualties commonly suffer blast injury (primary blast wave, thermal and chemical burns, penetrating fragment wounds, and blunt trauma) from high-energy munitions as well as penetrating trauma from high velocity gunshot wounds. The different mechanisms of injury and increased energy transfer that occur after military trauma may or may not result in different pathophysiological responses when compared with a civilian after a road traffic accident or stab wound. Understanding the admission coagulopathy profile of a military or civilian patient will help to inform future transfusion resuscitation protocols and may help to develop potential medical therapies that will be of benefit. This article summarises the authors' current understanding of the pathogenesis of ATC.

Clinical definition

The concept of ATC stems from the recognition that a prolonged prothrombin time (aPTT) and/or activated partial thromboplastin time (PT) at hospital admission, before resuscitation, is associated with a three to four-fold higher mortality rate and is independently associated with increased transfusion requirements, organ injury, sepsis and critical care length of stay [4]. In two large observational studies, one quarter of trauma patients had prolongation of PT and/or aPTT on admission, which was independently associated with bleeding and death [7]. The development of ATC occurs as a function of the extent of tissue damage and duration of shock.

The tests used to describe ATC have varied between studies, and have included standard plasma-based tests resulting in definitions based on abnormal: aPTT; PT; thrombin time (TT); international normalised ratio (INR); platelet count; fibrinogen level; disseminated intravascular coagulation (DIC) score of 1–4 (non-overt DIC) or ≥ 5 (overt DIC) or abnormalities in clotting amplitude and clot lysis in whole blood visco-elastic tests [5]. While there is as yet no universally accepted assay or definition, many experts use prolongation of the PT to indicate that there is, indeed, a coagulopathy. Ironically, the abnormal test results that have heightened our awareness of ATC may have contributed to well-intentioned but physiologically misguided therapeutic strategies.

Phases of ATC

There are different temporal phases in the evolution of ATC. The first phase is an immediate activation of multiple haemostatic pathways, including fibrinolysis, in association with tissue injury. The second phase is due to resuscitation-related factors, for example the use of colloids and red cells will dilute haemostatic factors; and post-resuscitation, there is an acute phase response leading to a prothrombotic state, predisposing to later venous thromboembolism. In some patients, especially if resuscitated late or inadequately so that there is continuing tissue hypoxia, DIC may ensue.

Immediate effects of tissue injury

The following may occur to varying extent depending on the type of tissue damaged, the type and extent of injury, predisposing to, or amplifying, ATC:

(1) *Consumption and loss.* Coagulation factors and platelets are consumed during the formation of extravascular clots and thrombus (thrombus is a clot formed within a vessel wall), as well as external loss from the intravascular compartment during bleeding. A reduction in circulating red cells has a major effect on primary haemostasis through reduction in axial blood flow. Red cells usually flow through the centre of an artery or arteriole, and platelets and plasma are pushed to the vessel wall, so that when a vessel is severed the necessary haemostatic factors are close by; this is disrupted once the haematocrit falls below about 30% [8], such that there is an inverse correlation between the haematocrit and in vitro bleeding time [9].

(2) *Dilution*. The reversal of Starling forces and consequent shifts of interstitial fluid into the vascular

compartment results in autodilution of haemostatic factors. This is aggravated by replacement of lost whole blood with crystalloid, colloid and red cell transfusion. Even so-called balanced transfusion strategies, such as 1:1:1, that attempt to deliver the functionality of whole blood with red cells, plasma and platelets in equal ratios, deliver a dilute final product due to the presence of anticoagulants and red cell additive solutions. The final 1:1:1 product has a haematocrit of 29%, a platelet count of about $80 \times 10^9.l^{-1}$ and coagulation factors diluted to 65% of normal. Ultimately, the resultant dilutional coagulopathy is proportional to the volume of fluid administered, both in vitro and in vivo [10, 11].

(3) *Hormonal and cytokine changes* follow tissue injury. The levels of cytokines and hormones such as epinephrine and vasopressin rise, hormone and thrombin production leads to endothelial cell activation (ECA). Tissue plasminogen activator (t-PA) and Weibel–Palade body contents are released from the endothelium after stimulation by vasopressin. Weibel–Palade bodies anneal with the endothelial wall releasing von Willebrand factor and exposing P-selectin present on their inner wall, onto the surface of the endothelial cell, enhancing platelet recruitment. Cytokines, such as TNF and IL-1 as well as thrombin and continued hypoxia, cause ECA and lead to a slow change in endothelial cell phenotype from antithrombotic to prothrombotic which, in inadequately resuscitated patients, leads to DIC. Endothelial cell activation down-regulates thrombomodulin and fibrinolysis, (PAI-1 levels increase) causing cleavage of glycosaminoglycans and sloughing of the glycocalyx from the cell surface, limiting activation of antithrombin; increases in platelet activating factor production increase endothelial permeability and, in vitro, up-regulates the expression of tissue factor [12, 13].

(4) *Hypoxia, acidosis* and *hypothermia*. This triad predisposes to bleeding by impairing the function of platelets and coagulation proteases while increasing fibrinolysis [14]. Hypoxia exacerbates ECA, and coagulopathic changes are most pronounced once the pH is < 7.1 [15] and core temperature is < 33 °C [16].

(5) *Immune activation*. Tissue damage and shock are associated with platelet release of soluble CD40-ligand, a potent immune activator that itself can cause further ECA and platelet activation, and is known to be necessary in order to stabilise thrombi [29]. Immune stimulation, including complement activation, is associated with release of damage-associated molecular patterns (DAMPs), such as mitochondrial DAMPs and histone-complexed DNA [30, 31]. Immune activation can aggravate tissue damage through mechanisms including proteolytic degradation and oxidative stress, thus amplifying haemostatic activation.

Pathophysiology

Current available evidence suggests that ATC is due to massive stimulation of thrombin generation, fibrinogen and platelet consumption, and fibrinolysis by damaged tissues. Tissue damage exposes tissue factor (TF), which is present on all cells within the body that are not normally in contact with the blood, and also the sub-endothelial matrix. Tissue factor drives localised thrombin and fibrin generation. Collagen within the sub-endothelial matrix binds to platelet glycoprotein VI and vWF to glycoprotein Ib, causing platelet activation. Activated platelets adhere to damaged tissues and serve as catalysts for amplification of thrombin generation. These processes are reflected in the findings of observational clinical studies that show reduced clotting factor and physiological anticoagulant levels [21–23], high thrombin generating capacity [3, 4, 21, 24–26] and reduced platelet counts [27, 28] Overall, these data indicate a consumptive coagulopathy. The most depleted coagulation factors are fibrinogen and factor V [22, 28], which are likely consumed in part by activated Protein C or free plasmin [29, 30], although the relative importance of these proteases in reducing factor levels remains unknown.

Thrombin is the key effector molecule in haemostasis; its generation not only converts fibrinogen to fibrin but, like a cytokine, it also activates platelets, leucocytes and endothelium. Thrombin is also a major stimulator of endothelial t-PA secretion, an effect previously known as secondary fibrinolysis (as fibrinolytic activation is secondary to coagulation activation). Stimulation of t-PA release from the endothelium by

other factors such as hypoxia, epinephrine and vasopressin, is known as primary fibrinolysis. High t-PA levels have been reported in coagulopathic trauma patients [4, 26]. In addition, when bound to the endothelial receptor, thrombomodulin, thrombin activates Protein C.

It has been proposed that activated protein C (aPC) is a major effector of ATC through cleavage of factors Va and VIIIa. In addition, by binding PAI-1 and de-repressing t-PA, it may activate fibrinolysis [3, 5, 29]. This mechanism is plausible but problematic due to the kinetics of the reactions. Platelets and plasma Factor Va are resistant to aPC cleavage at concentrations of aPC seen in ATC or even therapeutic use of recombinant human aPC in sepsis [31]. As a normal platelet count of 200×10^9 l^{-1} overcame aPC anticoagulant effects even at very high concentrations of aPC, and there was no detectable effect on fibrinolysis with or without platelets [31], it is difficult to envisage how aPC could drive the phenotype described as ATC. Furthermore, though factor V is depleted and PC converted to aPC in ATC, it has been amply demonstrated that thrombin generation potential is dramatically elevated in trauma patients; this is surely inconsistent with the notion that aPC is inhibiting thrombin generation by inactivating factor V [32]. Also, it must be noted that PAI-1 is a potent inhibitor of aPC in the presence of vitronectin [33]. It is unlikely that inactivation of aPC by vitronectin/PAI-1 would lead to PAI-1 depletion and acceleration of fibrinolysis, as PAI-1 circulates at about ten times higher levels than aPC [34, 35]. It seems more likely that the enormously increased release of t-PA due to epinephrine, vasopressin and thrombin signalling drives the fibrinolytic phenotype of ATC.

The CRASH-2 trial underscored the central role of fibrinolysis in ATC by demonstrating a one-third reduction in death due to haemorrhage in trauma patients given tranexamic acid (TXA), which inhibits activation of plasminogen to plasmin [36, 37]. Other clinical studies have reported that fibrinolytic activation is correlated with transfusions [38] and mortality [38–42]. The plasmin–antiplasmin complex (PAP) is perhaps the most sensitive indicator of fibrinolytic activation, and its levels are increased in approximately 60% of trauma patients [43]. Plasmin activation and generation of fibrin degradation products such as D-dimers [3, 4, 39, 44–46] are characteristic of bleeding trauma patients. Furthermore, free plasmin can break down coagulation factors, and the extent of this effect has not been fully evaluated in traumatic coagulopathy [47].

The pathophysiology of ATC evolves after the immediate haemostatic effects triggered by tissue injury. Endothelial cell activation, stimulated by thrombin and various cytokines, as well as hypoxia and hypoperfusion [48], generates a prothrombotic environment. Hypoperfusion plays a critical role in the pathogenesis of ATC as demonstrated in numerous clinical studies [3, 6, 42–51], animal models [6, 50] and in vitro experiments [22, 51]. These data indicate that as shock severity increases, the PT and INR rise [4, 5, 7, 52] and coagulation factor levels fall [6, 48]. The most compelling of these studies, that included 3646 patients, demonstrated that ATC (INR > 1.2) occurred only when significant hypoperfusion (base deficit > 6 $mmol.l^{-1}$) was combined with severe injury (Injury severity score > 15) [6].

As ATC evolves over time, the prothrombotic effects of endothelial cell activation eventually predominate, particularly if hypoxia and acidosis are not alleviated. Many factors contribute, but release of phosphatidylserine positive microvesicles from the endothelium exacerbates the prothrombotic environment [53]. A net production of PAI-1 over t-PA further leads to shutdown of fibrinolysis [4, 25, 45]. This may explain why antifibrinolytic treatment at this stage may worsen outcome [40].

Platelets form the scaffold of clots during primary haemostasis, and serve as the catalysts of coagulation in the current cell-based model of coagulation. Platelets are relatively unresponsive to collagen, ADP and arachidonic acid after trauma [54, 55]. The pathophysiology underlying this dysfunction, which remains obscure, probably explains improved outcomes associated with platelet transfusion despite adequate platelet counts [56, 57]. Lower platelet counts on hospital admission predict trauma mortality, even when within the normal range [58, 59]. Furthermore, outcomes may be determined by the quality of transfused platelets [60].

Cellular microvesicles also contribute to normal haemostasis. Tissue factor initiates clot formation

when P-selectin glycoprotein ligand 1 (PSGL-1)/TF-bearing microvesicles from monocytes interact with P-selectin on platelets attached to injured tissue [61]. This procoagulant microvesicle production increases in trauma [62] and accelerates prothrombotic change [63].

In some ways, the initial changes of ATC are similar to DIC [40, 64]. However, in most trauma patients, there is no evidence of inappropriate disseminated clot formation on histological examination [65], so early ATC is not DIC.

The importance of rapidly identifying coagulopathy

Severely injured patients are more likely to suffer from haemorrhagic shock, require massive transfusions, and are at high risk of death due to bleeding. Acute traumatic coagulopathy is the key pathophysiological derangement, driven by tissue damage, which results in TF exposure, shock and hypoxia, and must be mitigated to successfully resuscitate the patient [66, 67].

Predicting coagulopathy

Scoring systems have been developed for adult and paediatric trauma populations that predict which patients will develop severe haemorrhage and require massive resuscitation. Algorithms based on these scores shift clinical management from a reactive to a proactive stance [66–71]. Unfortunately, none of these scoring systems identify all patients at risk of ATC and death due to bleeding. Therefore, it should be assumed that any patient considered at risk of exsanguination is at risk of ATC and death [70].

Current methods for ATC diagnosis and their pitfalls

Standard coagulation tests

These include PT-based tests (PT, INR), aPTT and Clauss fibrinogen. The PT/INR is considered an adequate screen for multiple coagulation factor deficiencies, and was thus adopted as a marker of ATC [28]. Every laboratory can provide PT, aPTT and fibrinogen results, and they are useful in guiding transfusion and predicting mortality [51].

Originally, these tests were designed to evaluate clotting factor deficiencies, not acquired multiple factor-based coagulopathies, and they are not predictors of bleeding in these circumstances [72]. Moreover, they do not take into consideration the contribution of platelets to haemostasis, the role of fibrinolysis, thrombin generation, or the interactions between coagulation enzymes and cellular phospholipid surfaces. Furthermore, these are not point-of-care assays and turnaround times often negate the value of the results [5]. Therefore, plasma-based coagulation assays are rarely helpful in the immediate management of ATC, but they do have an important role in monitoring ongoing bleeding, to guide the use of appropriate blood products.

Thromboelastography and thromboelastometry

Increasingly, TEG® (Hemonetics Corporation, Braintree, MA, USA) and ROTEM® (TEM International GmbH, Munich, Germany) are being used to guide trauma resuscitation [38, 41]. Minimally injured patients tend to have normal profiles, whereas moderately or severely injured patients typically exhibit TEG changes [38, 46]. Thromboelastograpy and ROTEM can play a role in the diagnosis of severe fibrinolysis, but are insensitive to more limited fibrinolytic activity [73]. Marked fibrinolysis detected by TEG or ROTEM is associated with a poor prognosis. Schöchl et al. [41] and others have defined hyperfibrinolysis as a reduction in maximal amplitude (MA) of 15% on ROTEM testing. However, this definition conflicts with the classic understanding of hyperfibrinolysis, which describes a kinetic reversal whereby fibrinolytic activity is greater than fibrin formation, and clot strength is compromised [74]. Thrombolastographic hyperfibrinolysis should perhaps be used to describe increased lysis only in relation to TEG visco-elastic measurements.

There is no commonly accepted visco-elastic definition of ATC, although the candidates include: increases in clotting time and clot formation time; and loss of clot amplitude (CA) and maximal clot amplitude [40, 50, 75]. One group used ROTEM to define an EXTEM CA5 (CA at 5 min) value of < 36 mm as diagnostic of ATC [5]. Another group suggests that TEG or ROTEM A10 correlates well with platelet count and fibrinogen level and predicts transfusion requirements. Advocates for visco-elastic monitoring suggest that the capacity to distinguish specific haemo-

static abnormalities provides a means of individualising coagulation and transfusion management [37, 41]. However, there are no ROTEM and TEG algorithms validated by randomised trials. Another important limitation is that, like other standard coagulation tests, TEG and ROTEM are typically performed at 37 °C, and results underestimate coagulation disturbances in hypothermic patients.

The evolving importance of ATC in trauma resuscitation

The recognition of ATC has driven dramatic change in trauma management. Until the military experience in Iraq and Afghanistan was published over the last 10 years, resuscitation was started with red cell concentrates, and scant attention was paid to coagulopathy until much later. Retrospective data from the USA and UK military and leading civilian institutions described improved outcomes in those treated with fresh whole blood [76–78] or fresh frozen plasma (FFP), cryoprecipitate and platelets in combination with red cells and tranexamic acid, with extremely limited use of colloid or crystalloid infusions [76–82], a practice known as haemostatic resuscitation [83]. It is possible that current transfusion strategies can be optimised to further improve survival after ATC [84]; the results of randomised controlled trials will guide further developments [85]. In North America, the challenge of managing ATC has generated renewed interest in whole blood for trauma resuscitation [86–89]. On the other hand, in some European countries, fibrinogen and other factor concentrates have replaced FFP in the management of ATC [90]. The evolution of divergent clinical practices underscores the need for a better understanding of the pathophysiology of ATC and for more clinical research looking at the full risks and benefits of improved haemostatic management. For example, there are no studies looking at the effect of modern treatment on the rate of post-trauma venous thromboembolism, which is a major cause of morbidity and mortality. It is recognised that the use of prothrombin complex concentrate may induce later prothrombotic changes [91], and potentially this may affect the rate of posttrauma thromboembolism.

Conclusion

Over the last decade, the incidence and implications of ATC have become clearer to the trauma community. Further clinical studies are required to increase our understanding of the pathophysiology of traumatic coagulopathy and inform the direction of studies to improve haemostatic management and outcomes.

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Competing interests

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